

Original Article

Comparison of postoperative values for C-reactive protein in minimally invasive and open lumbar spinal fusion surgery

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Abstract

Background: A major purported benefit of minimally-invasive spinal surgery (MIS) technique is less disruption of paraspinal soft tissues, but there is little quantifiable evidence of this in medical literature. Postoperative C-reactive protein (CRP) levels been shown to become more significantly elevated with larger surgical procedures, and this may allow for more measurable appreciation of any benefits of MIS verses open spinal surgery.

Methods: CRP values were measured prior to and at multiple time points following surgery in patients undergoing posterior spinal fusion using both open and minimally invasive techniques.

Results: Peak postoperative CRP was significantly lower in the 35 single-level minimally invasive procedures compared with the 11 single-level open procedures (13.5 vs. 21.3, $P < 0.01$) and lower in the 12 two-level minimally invasive surgeries compared with 16 two-level open procedures (20.5 vs. 31.8, $P < 0.01$).

Conclusions: MIS lumbar fusion is associated with a lower peak in postoperative CRP compared with open surgery. This appears to support the notion that minimally invasive spine surgery technique leads to a measurable reduction in paraspinal soft tissue destruction mediated inflammation in the immediate postoperative period.

Key words: C-reactive protein, infection, lumbar fusion, minimally invasive surgery, prospective, spine surgery

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INTRODUCTION

Minimally invasive surgery (MIS) techniques are rapidly gaining popularity to treat a variety of spinal conditions. MIS procedures typically achieve exposure of the spine via tubular access ports placed after sequential, blunt, muscle dilation rather than wide dissection of paraspinal tissues and the purported advantages include reduced blood loss and postoperative pain. In addition, it has

been suggested that MIS may lower the incidence of postoperative infections.^[2,3]

C-reactive protein (CRP) is a non-specific marker of inflammation that has been shown to be valuable in the diagnosis of postoperative infections and for surveillance during treatment of established spinal infections.^[6-8,10] CRP is manufactured in the liver and the normal plasma level is less than 1 mg/L. Within a 4-6 hr after initial tissue injury levels begin to rise. CRP half-life is less

than 24 hours, and levels return to normal much faster than the erythrocyte sedimentation rate (ESR) making it more attractive as a marker of active inflammation or infection.^[4-6,8,16] Normative values following lumbar spinal fusion surgery have not been definitively established, but evidence suggests that the peak values increase with the extent of surgical tissue destruction.^[12,15] Al-Jabi noted that following neurosurgery, extent to which postoperative levels of CRP are elevated seem to depend upon the magnitude of the procedure.^[1] Reduced soft tissue dissection in minimally invasive lumbar fusion may lower the expected values of postoperative CRP when compared with conventional open surgery, and awareness of any such difference may prove helpful in assessing infectious complications.

In this prospective study, we recorded the value of CRP prior to and at multiple time points following surgery in patients undergoing posterior spinal fusion using both open and minimally invasive techniques. Statistical analysis was employed to compare the results of these two groups as well the results of subgroups undergoing single or two-level surgery.

MATERIALS AND METHODS

Over an eighteen month period at a university tertiary care center, patients undergoing one or two-level lumbar fusion with instrumentation had CRP tested prior to surgery and postoperatively at days 1, 3, 7, and at subsequent 3-week intervals until normalized. Indications for surgery were lumbar stenosis with spondylolisthesis; radiculopathy with foraminal stenosis, foreshortening of the disc space, and facet arthropathy; and recurrent disc herniation. Selection of operative technique was based upon surgeon preference. The majority of open surgery patients were treated in the early months of the study period before the senior authors practice had principally shifted to minimally invasive technique. Data was compiled on patient age, sex, level of surgery, medical comorbidities, and history of prior lumbar surgery.

MIS surgery was accomplished through a paramedian incision, typically 4cm off the midline, utilizing a blunt, muscle-splitting approach using a tubular dilators prior to placement of a working channel anchored to the OR table. All MIS patients underwent transforaminal lumbar interbody fusion (TLIF) with total or partial laminectomy, placement local autograft supplemented with cancellous allograft chips in the anterior third of the disc space, and interbody placement of a polyetheretherketone (PEEK) spacer filled with a portion of BMP-2 sponge (infuse, Medtronic Inc., Minneapolis) sized to loosely fit the cage cavity. The intertransverse gutter was not exposed for graft placement. Internal fixation with bilateral titanium pedicle screws was then inserted percutaneously under fluoroscopic guidance. The skin incision for a single-level

MIS procedure was typically 28-30mm, and was extended several millimeters for the two-level procedures. Surgical drains were not used in any MIS patient.

Patients treated with open surgery underwent a midline incision and laminectomy followed by traditional posterolateral, intertransverse fusion with local autograft supplemented with allograft cancellous chips and bilateral pedicle screw instrumentation. Three single-level open fusion patients also had placement of a PEEK interbody spacer filled with local autograft in addition to the graft in the posterolateral gutter. Subfascial surgical drains were placed in all open surgery patients and typically removed on the second postoperative day.

Any infectious complications were noted and excluded from analysis. Commercially available software (Graphpad Prism 4, Graphpad Software Inc., San Diego CA) was used to generate descriptive statistics analysis. The Mann-Whitney test was used to compare the peak values of CRP of patient subgroups.

RESULTS

Eighty-nine consecutive patients underwent surgery. Excluded from analysis were nine patients in whom a baseline CRP value failed to be drawn, three patients that failed to follow up with a minimum of three postoperative blood draws, and three patients that developed postoperative infections. The remaining 74 patients were the basis of the study, out of whom there were 41 female and 33 male patients a mean age of 59. Eight patients had undergone prior lumbar surgery, four of 27 (14%) patients undergoing open surgery and four of 47 (8%) of those undergoing MIS procedures. Fifty-two (70%) had lumbar spinal stenosis with a spondylolisthesis, sixteen (21%) had radiculopathy with foraminal stenosis associated with disc space foreshortening and facet arthropathy, and six (8%) had recurrent disc herniation. Demographic data and medical comorbidities of the four subgroups assessed in this study are detailed in Table 1.

Data was collected according to protocol in only 40% of patients, with many patients missing specimen collection on the appropriate date and having additional collections on earlier and later days [Figure 1] Most of the deviation from protocol took place at the one and three week intervals, while over 80% of the day one and day three tests were successfully collected. Peak postoperative CRP was significantly lower in the 35 single-level minimally invasive procedures when compared with the 11 single-level open procedures (13.5 vs. 21.3, $P < 0.01$) [Figure 2] and lower in the 12 two-level minimally invasive surgeries compared with 16 two-level open procedures (20.5 vs. 31.8, $P < 0.01$). [Figure 3]. Detailed statistical data comparing subgroups is displayed in Tables 2 and 3. Peak value of CRP occurred at a mean 2.9 days after surgery

Table 1: Demographic and comorbidity data for patients undergoing lumbar decompression and fusion using either minimally invasive surgery or Open techniques

	Open single-level	MIS single-level	Open two-level	MIS two-level
Patients	11	35	16	12
Mean age	58	57	63	59
Male (%)	6 (54)	16 (46)	5 (31)	6 (50)
Female (%)	5 (46)	19 (54)	11 (69)	6 (50)
Hypertension (%)	2 (18)	5 (14)	7 (44)	2 (17)
Diabetes (%)	1 (9)	5 (14)	4 (25)	2 (16)
Rheumatoid arthritis (%)	0	1 (2)	1 (6)	0
Fibromyalgia	0	0	0	0

MIS: Minimally invasive surgery

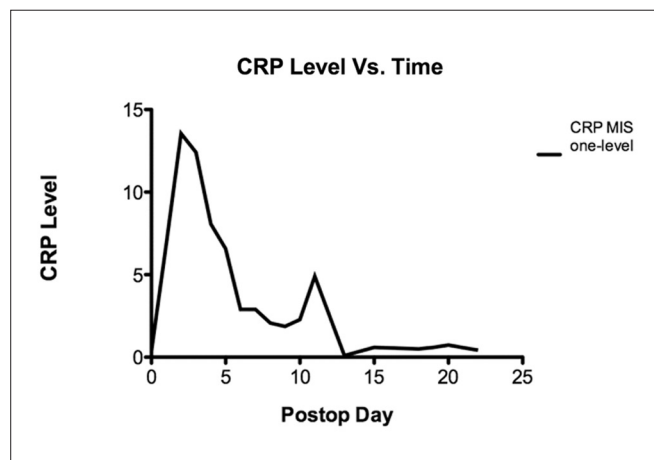


Figure 1: A graph demonstrating the value of C-reactive protein verses time following single level minimally invasive transforaminal lumbar interbody fusion procedures. The C-reactive protein rises rapidly to a peak generally seen at the third postoperative day after which it rapidly declines. Increasing C-reactive protein values subsequent to the fourth postoperative day should raise suspicion of a surgical infection

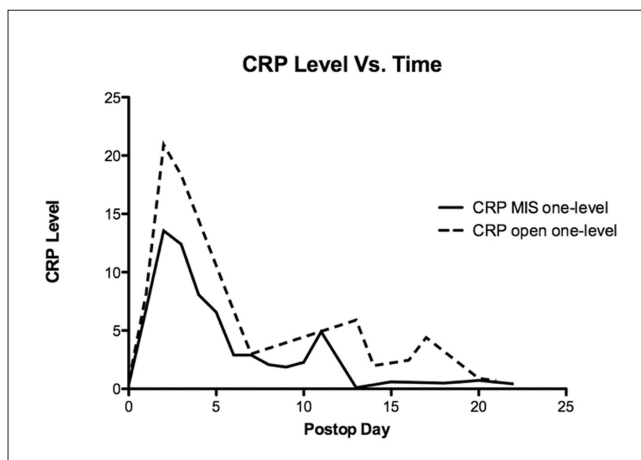


Figure 2: The peak value for C-reactive protein was significantly lower in patients undergoing single-level minimally invasive lumbar fusion (thick solid line) compared with open single-level lumbar fusion (thin solid line) ($P<0.01$)

Table 2: Statistical analysis of peak values of C-reactive protein in subgroups undergoing single-level open and minimally invasive surgery lumbar decompression and fusion surgery

Peak CRP Values	Open single-level	MIS single-level
Patients	11	35
Minimum	12.0	4.1
Maximum	27.0	31.0
Mean	21.3	13.5
Median	21.0	11.7
Standard Deviation	5.0	8.2
Lower 95% Confidence Interval	17.9	10.6
Upper 95% Confidence Interval	24.6	16.4

CRP: C-reactive protein, MIS: Minimally invasive surgery

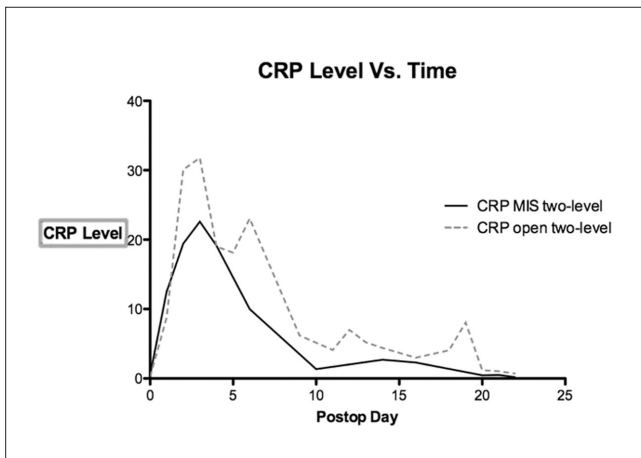


Figure 3: The peak value for C-reactive protein was significantly lower in patients undergoing Two-level minimally invasive lumbar fusion (thick broken line) compared with open two-level lumbar fusion (thin broken line) ($P<0.01$)

Table 3. CRP data in two-level open versus minimally invasive transforaminal lumbar interbody fusion procedures

Peak CRP Values	Open two-level	MIS two-level
Patients	16	12
Minimum	14.0	6.6
Maximum	51.0	34.5
Mean	31.8	20.5
Median	31.5	21.7
Standard Deviation	10.5	9.0
Lower 95% Confidence Interval	26.2	14.4
Upper 95% Confidence Interval	37.4	25.7

and there was no significant difference in timing of peak values between various subgroups [Figure 4].

Three patients suffered infectious complications: two subfascial infections in the two-level open group and one superficial infection in the single-level minimally invasive group. In the two deep infections, each of which necessitated operative debridement, CRP levels remained persistently elevated at three weeks post surgery, gradually returning to normal over prolonged courses of intravenous antibiotics. The superficial infection, which occurred in a patient after single-level minimally invasive fusion, presented with wound drainage and erythema at postop day seven; but the CRP was 1.3, only slightly above the upper limit of normal at 1.0, and within the range seen in the other patients in the single level MIS group at the same point in time.

DISCUSSION

A major theoretical benefit of minimally invasive spinal surgery technique is reduction in disruption of paraspinal soft tissues. There is little objective and quantifiable evidence in medical literature, however, to support this supposition. Stevens *et al*, examined postoperative MRI in patients undergoing conventional open and minimally invasive lumbar fusion surgery and found less T2 signal indicative of paraspinal edema in patients that had undergone MIS procedures.^[14] Sasoka *et al*, compared the values of a panel of laboratory makers of inflammation including CRP in patients undergoing open versus minimally invasive single-level discectomy or laminotomy and found that the MIS patients had significantly lower values in the early post-operative phase.^[12]

Our findings of significantly reduced peak values for CRP in MIS lumbar fusion procedures compared with open surgery supports the notion that there is measurable reduction in tissue destruction-mediated postoperative inflammation in MIS surgery. In addition, the pattern of decline in postoperative CRP values seen in this study may help in understanding normative values for MIS

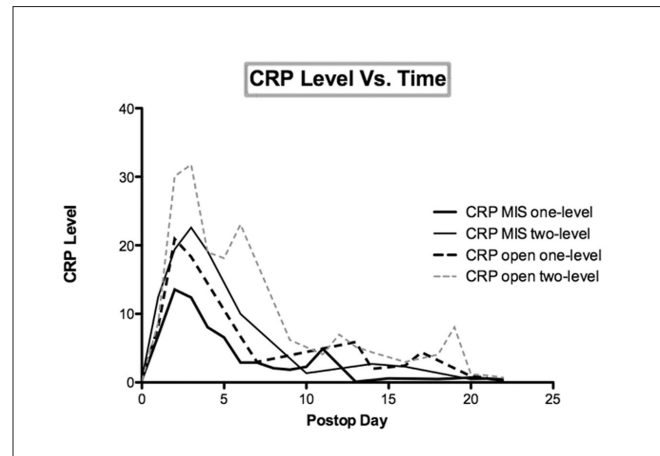


Figure 4: Postoperative C-reactive protein values for all four subgroups peaked at approximately the same duration of time following surgery. There was no statistical difference in the time necessary to return to normal values among the subgroups

fusion surgery; and this may provide useful information when assessing a possible postoperative infection.^[8]

A weakness of the study was the lack of rigid adherence to the study protocol. Although the study number permitted statistical analysis of the results, it is possible that better compliance with the protocol might have affected our results. Another potential confounding variable in interpreting our results would be the presence of any factors leading to elevated CRP beyond typical postoperative values. These would include infection, which was carefully excluded in this study, and activation of non-infectious etiology such as vasculitis or gout, though we did not identify patients with these conditions in the study.

One factor not controlled in this investigation was the use of bone morphogenic protein 2 (BMP-2). BMP-2 was used as the osteoinductive graft material in all patients in the MIS group and not used at all in the open surgery group. It is known that there is a substantial induction of tissue inflammation mediated by BMP-2 in the initial postoperative period, and the effect its use upon the systemic levels of CRP, if any, are not known.^[9,11,13] Robin showed that local seroma fluid after posterior cervical fusion surgery contained impressive elevations of cytokines, especially IL-6 and IL-8. Thus, it can be speculated that the effect of BMP-2 use may have served to reduce rather than magnify any difference in CRP between the open and MIS groups and would not diminish the significance of our findings.

In conclusion, minimally invasive single and two-level posterior lumbar fusion surgery is associated with a lower peak in postoperative CRP compared with open surgery. This appears to support the notion that minimally invasive spine surgery technique leads to a measurable reduction in paraspinal soft tissue destruction mediated inflammation in the immediate postoperative period.

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Commentary

Minimally invasive spine surgery (MIS) is presumed to offer clinical benefits due to limited tissue dissection and injury. Elevations in C-reactive protein (CRP), a nonspecific marker of inflammation, are commonly cited when making the diagnosis of a postoperative infection. In an attempt to quantify the reduction in tissue injury associated with MIS posterior lumbar interbody fusion, the authors have chosen to trend postoperative CRP levels following MIS and open one- or two-level posterior lumbar interbody fusions. In both instances, CRP levels were significantly lower in the MIS group when compared with those in the open procedure group.

This study is strengthened by the sample sizes and length of time over which CRP values were collected. The authors conclude that their findings support the existing belief that MIS is associated with significantly reduced tissue destruction and postoperative inflammation. Unfortunately, the true clinical relevance of postoperative CRP values is unknown, thereby limiting meaningful interpretation of the data.

Elevated CRP values are routinely used as an indicator of active infection within clinical practice. Intuitively, based on the present understanding of the inflammatory process, increased intraoperative tissue destruction would be associated with proportionally greater CRP values. However, the significance of elevated CRP values in the wake of surgery is largely unknown, and the utility of

CRP as a marker of mechanical tissue injury remains unproven.

The parameters differentiating various degrees of tissue destruction, as well as the relationship between tissue injury and an associated rise in CRP, have not been defined. Further clouding the relevance of CRP, as the authors discuss, is the lack of a normative range of CRP levels following lumbar surgery. It becomes difficult to apply this variable to a discussion of tissue injury severity, which itself is ill-defined and deficient in standardized criteria. Differences in CRP values may represent a poor tool by which to quantify reduced tissue injury in MIS lumbar fusions.

Other clinical outcomes could be considered and relation to elevated CRP levels investigated. The authors did not discuss the length of hospital stay or postoperative pain in either group, both of which are thought to be decreased in MIS lumbar fusion. If a reduction in CRP values accurately reflected a reduction in tissue injury, then it would have been useful to show a correlation with clinically relevant outcomes.

Additionally, despite the significant reduction in CRP values following MIS, there was no significant difference in the number of infections between the groups. Further weakening the conclusion is that the CRP value found in the infected MIS patient was near normal and within the range of CRP values seen in MIS patients without

infection. These findings suggest that any reduction in tissue injury associated with reduced CRP levels may be of limited clinical significance.

Despite some questions with the methodology employed in this study, we believe that this paper makes a significant addition to the literature. As we and the authors have stated, there is a lack of knowledge pertaining to the normative CRP values following MIS posterior lumbar interbody fusion. The trends in postoperative CRP values reported in this paper contribute to our current understanding of these values and provide a reference

for more meaningful interpretation of lab values within clinical practice. Analysis of the relationship between postoperative CRP values and use of bone morphogenetic proteins would also be of interest. Further analyses are necessary to clarify the normative range of CRP values at multiple time points and in all spine procedures.

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Commentary

Inflammatory markers in spine fusion surgeries

Minimally invasive spine surgery (MIS) has recently been popularized due to the development of tubular dilators and associated instrumentation. The technique has gained favor due to the decreased tissue disruption, patient morbidity, and hospital stays that result. While socioeconomic and patient outcome data are relatively straightforward to collect with regard to MIS procedure benefits, more objective marker data are not as emphasized in the literature. The authors propose and undertake a more objective approach to proving the benefits of MIS. They conduct an observational study of 47 MIS and 27 open spinal procedures and found that C-reactive protein (CRP) peaks were consistently lower in the MIS group with high statistical significance ($P < 0.01$). We applaud the authors for their creativity with regard to approaching the question of finding more objective evidence to prove the benefits of MIS.

There are, however, several points we would like to address. Weaknesses of the study include the lack of thorough follow-up according to the outlined methods. Data were collected according to the protocol in less than half of patients. In their discussion, the authors do include the study by Sasaoka *et al.* who did review CRP values.^[19] However, there are two other previous studies that they did not include in their discussion. Chao *et al.* reported their study of 44 patients in 2007 showing similar results with serum CRP levels peaking at 24 h for the MIS group and peaking at 48 h for the open group.^[17] The CRP for the MIS group peaked at 12.68 ± 7.10 mg/L. The CRP for the open group peaked at 29.95 ± 14.85 mg/L. The results were statistically significant ($P < 0.05$). Huang *et al.* reported a prospective randomized controlled trial of 22 patients in which the open procedure patients had a statistically significant greater rise in CRP levels: $27.78 \pm$

15.02 versus 13.84 ± 6.25 mg/L ($P = 0.026$).^[18] Although previous trials have been performed and even randomized controlled trials have been reported, we believe that this study does provide a good contribution to the literature, even if it is not completely novel.

Another important consideration was that the study was not controlled with regard to BMP use. BMP has been noted to have effects of immunogenicity and inflammation. The fact that BMP use may cause some variances in the data in such a small study is the cause for concern. BMP-2 was used in all MIS cases but not in any open procedures. The authors speculate that the effect of BMP-2 may be a proinflammatory response, although this has not been borne out in the literature, and then go on to state that its use might have served to reduce rather than magnify the difference in CRP levels between the open and MIS groups. This is an assumption and such a proposal should be treated with caution until these facts are supported by clinical data.

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